THE CONCEPT OF "ALLERGY"*

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THE term "allergy" was coined by Clemens von Pirquet in 1906. This was almost 70 years ago. To emphasize how long ago 1906 was medically, it should be realized that there is a longer time span between von Pirquet and us than between von Pirquet and the beginning of modern medicine—modern medicine is said to have begun with Pasteur and Koch and the demonstration of the bacterial causation of disease. Only 24 years separate Koch's discovery of the tubercle bacillus from von Pirquet's concept of allergy. Beyond discovering the causes of a large number of infectious diseases, Pasteur and Koch both played a leading role in the development of immunology, studying, among other things, the prevention of disease by immunization.

Pasteur's prophylaxis for rabies has not changed much over the years; certainly the concept has not changed. Koch failed in his attempt to immunize against tuberculosis, but it was a glorious failure in that it greatly furthered the understanding of the nature of the reactions that went on in the body during the development of an infectious disease. By virtue of furnishing a clear demonstration of the alteration in reactivity in preinfectious and postinfectious states, it also provided a major stimulus for von Pirquet's thinking. With the overwhelming advances introduced by the discovery of specific microbial causes for a large number of diseases a rather simplistic view of disease developed. Basically this view attempted to correlate each morbid entity with a single exogenous cause. It was further believed that in infectious diseases the symptoms were dependent solely on adequate multiplication of the invading microorganisms. What was needed was realization of the dual nature of infectious disease: namely, that the organism and the host interact to produce the signs and symptoms.

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Ever since medicine began it had been realized that different bodily states influenced or determined the symptoms of disease. In 1881 Jonathan Hutchinson gave six lectures on temperament, idiosyncrasy, and diathesis and their influence on disease. These were subsequently published as a book called *The Pedigree of Disease*, yet these concepts were basically metaphysical. None had been forged in the crucible of experimentation. They were, as has been said: a mass of Latin words falling upon the facts like sòft snow, blurring the outlines and covering all the details.

Von Pirquet, on the other hand, based his views on carefully documented clinical studies and some experiments. His ideas opened the way for a deeper understanding of disease. Not only did he demonstrate that symptoms depended on both cause and host, but also that the stimulus itself could alter the body so that upon subsequent exposure to the same or to an immunologically closely related disease the body would react differently. Von Pirquet realized that many of the manifestations of a disease were due to an alteration in reactivity and not to the exogenous stimulus per se.

Before considering von Pirquet's definition of allergy, I shall briefly consider definitions and some consequences that flow from defining an object or an event. First, there are various kinds of definitions: namely, ostensive, operational, and denotative. An ostensive definition explains the nature of the object to be defined without the use of words. Suppose it is asked what a certain color, say "beige," is and an object that is considered to be beige-colored is pointed to; that would be an ostensive definition. An operational definition defines the term by performing the act that is inquired about. For example, if it were asked what is meant by differentiation in mathematics, a demonstration of differentiating the function would be an operational definition; on the other hand, if a verbal description of how this is done were given, that would be a denotative definition, which is the usual kind of definition that we employ and the kind I shall be talking about.

A denotative definition is one that explains the object or event by words. It substitutes one set of words for another, which, in one sense, makes it vacuous, in that words are defined by other words. If this is followed to its ultimate conclusion there must be undefined words or there is complete circularity. For example, if the word "beautiful"

is looked up in the dictionary and is found to mean handsome, and then the word "handsome" is looked up and it is defined as beautiful, one has come to a dead end. This is always true of denotative definitions, but they are usually adequate because ordinarily it is sufficient to define an abstract term by terms less abstract. It is then believed that a better understanding of the original term is had; in general this is true.

Further, it must be remembered that a definition is a description. Of itself, it does not advance knowledge of the event. Its function is to provide a convenient label so that, rather than having to go into a long description, the name which is the label for the definition can be substituted. Thereby much time is saved. A person hearing or seeing the label, provided he knows the definition of that label, is then competent to envision for himself the phenomenon under discussion. Unfortunately, this tends to put a straitjacket upon thinking, because there is a feedback from the definition that causes thought to flow in regimented channels which do not allow for deviations. Definitions have an influence analogous to that described by Cicero, who said, "Often the greatest obstacle to those who want to learn is the authority of those who teach." It would be simpler, but somewhat chaotic, if we took the attitude of Humpty Dumpty in *Through the Looking-Glass*, who said, "When I use a word, it means just what *I* choose it to mean—neither more nor less."

A final problem with denotative definitions is that, as more insight is obtained concerning the nature of the phenomenon being defined, the definition needs to be altered so that it describes the phenomenon more accurately in the light of newer knowledge. This is one of the problems with von Pirquet's definition of the word allergy. In this connection I should like to remind you of Sir Arthur Eddington's wise comment. In discussing cosmological theories, the great astrophysicist said that they were like picture frames. A new one fitted the picture more precisely. This did not mean that the old one was wrong, but only that with newer knowledge the picture can be measured more accurately and hence a frame with a nicer fit provided.

Von Pirquet defined allergy as an acquired specific alteration in the capacity to react. Both hyperreactivity and hyporeactivity were included in this concept, but no mechanism was described. While this was an extremely important seminal concept, in my opinion its scope

was too broad. Because of its breadth there was, and still is, vagueness as to what should be included. To illustrate this, in the first issue of the *Journal of Allergy*, which made its appearance in November 1929, the editors felt it necessary to start with an announcement of what they meant by the word allergy. They said:

> In view of the wide differences of opinion as to how the word "allergy" should be used, we have felt it necessary to set forth the sense in which the term is used in the title of this journal.
>
> We believe it evident that it does not possess an established meaning and scientific usage. However, the term is very generally employed by clinicians, who apply it to conditions of specific hypersensitiveness exclusive of anaphylaxis in lower animals.

It is somewhat unfair to criticize this pronouncement at a distance of 45 years; yet I feel it worthwhile to point out that the editors of the first American journal dealing with the subspecialty of allergy provided almost no concept of what allergy included and no concept whatsoever of the mechanism by which the allergic reaction was brought about. Moreover, the definition concluded with a major error in classification. This fuzziness has persisted through the years and has served to muddy the clinical waters from which so-called allergic conditions are fished.

As already mentioned, the major difficulty with von Pirquet's definition is that it is too inclusive. It reminds me of the word "culture," which has been described as "one of those words which illustrates the law of accelerating fuzziness. It is a notion which grows by feeding on itself until in the end it encompasses so much that it designates precisely nothing." All kinds of acquired alterations in reactivity were embraced in von Pirquet's definition. There was no specification of the mechanism by which the altered reactivity was brought about. Partly because of the breadth of the concept and partly because of the vagueness of the mechanism many heterogeneous conditions have been classified as allergic. For example, by von Pirquet's definition an acquired tolerance to various drugs, such as alcohol or barbiturates, would be an example of allergy. I do not believe that many present-day physicians would wish to include such phenomena under that caption.

TABLE I. SKIN CONDITIONS USUALLY REGARDED AS ALLERGIC.

Reasonably certain allergic skin conditions
1) Dermatitis venenata—some
2) Urticaria—some
3) Purpuras—some

Questionably allergic skin conditions
1) Drug reactions
2) Ids
3) Vasculitides
4) Physical allergies
5) Multiform erythemas

"Nonallergic" allergic skin conditions
Atopic dermatitis

The problem is to find the mechanism for all forms of acquired alteration in the capacity to react, and then to formulate a definition which fits the varieties that have a common pathogenesis, yet which excludes those that are brought about by a different mechanism. A somewhat naive solution was to say that all forms of altered reactivity that were based on an immunologic mechanism were allergic, but such a definition only substitutes for the problem of defining allergy that of defining immunologic. Later it was thought that if von Pirquet's definition were modified by adding as a final phrase, "brought about by an antibody mechanism," this would solve the problem. However, it soon became clear that there were many biologic phenomena which appeared to be of an immunologic nature and which were regarded as allergic, yet in which no antibodies could be found: e.g., contact dermatitis from poison ivy. By an antibody was meant a modified serum protein, usually a gamma globulin.

Today it is believed that the basic change in the development of the altered state of reactivity that is classified as allergic is probably either the selection of a specific B or T lymphocyte or an alteration in lymphocytic behavior. Admittedly, little or nothing is known as to how a specific clone of lymphocytes is selected or by what means their behavior is modified; consequently, basic knowledge of the fundamental alteration in the development of an allergic state is still lacking, but within a few years it will probably be at hand, and a more precise definition of allergy will then be possible.

As a working hypothesis, I shall define allergy as a specifically acquired alteration in reactivity brought about by the selection of specific lymphocytes or by a modification in the reactivity of these cells when they encounter a specific configuration. I hasten to admit that there are many defects in this definition, but to me it seems to fit better than von Pirquet's original definition and subsequent modifications of it.

I shall now consider various skin conditions usually regarded as allergic. Table I lists these and categorizes them as I view them with respect to the legitimacy of the label "allergic." I do not anticipate much contention about the legitimacy of conditions in the "reasonably certain" category. These also may be classified as primary allergic conditions which are skin lesions that develop as a sole consequence of the allergic (immunologic) reaction; hence, the allergic reaction is a necessary and sufficient condition for the production of the skin lesions. The importance of this is that if the allergic reaction is interfered with or prevented the skin lesions either will not appear or will disappear. A classic example of this is an eczematous reaction to poison ivy.

The group labeled "questionably allergic skin conditions" includes drug reactions, "ids," vasculitides, physical allergies, and multiform erythemas. First, it is probable that those within the above category, while having some clinical and pathologic kinship, actually include pathogenetically unrelated conditions, so that persons to whom the above labels are given in reality comprise a heterogeneous group. Consequently, if for any member some clinical examples develop by way of an allergic mechanism, not all do. In truth, for most of them there is not enough information available concerning their pathogenesis upon which to base an opinion; hence, until more information is forthcoming, it is not really possible to decide whether they warrant the title allergic. I shall not discuss further the vasculitides, physical allergies, and multiform erythemas, but I shall comment on both drug reactions and ids.

Table II displays the possible responses to a drug. If the classification of responses to drugs given in Table II is correct, it is obvious that the majority of reactions to drugs do not have an allergic basis. Apart from intellectual satisfaction, it is very important practically to realize this, as in general the treatment that is of value for an allergic reaction will not necessarily be valuable in one brought about by another mechanism. More important, there has been much pseudode-

TABLE II. POSSIBLE RESPONSES TO A DRUG

Pharmacologic
1) Usual
   a) Desired
   b) Undesired side effects
2) Deviant
   a) Biochemical
   b) Anatomical

Allergic

sensitization to drugs, which was at best useless and at worst fatal, by furnishing an iatrogenically induced false sense of security.

Let me consider Table II in somewhat greater detail, beginning with the undesirable pharmacologic effects or side effects. These are normal pharmacologic concomitants of the use of the drug but are undesired effects at that time in that patient. Someone has stated, cynically but perceptively, that the side reactions of yesterday are the drugs of today, but the drugs of today are the malpractice of tomorrow.

I suspect that most drug reactions which are labeled allergic are really examples of biochemical deviation. A great advance in medicine was achieved when the primaquine story was elucidated; evidence was provided showing that some persons reacted differently to primaquine because of a deficiency of a specific enzyme or a deviant form of this enzyme. Since that day an entire new branch of medicine has developed: pharmacogenetics. I believe that from this will come one of the most important aspects of drug utilization. It may be that in the future patients will be typed for enzymatic reactivity to various categories of drugs, so that it will be known whether they can tolerate a certain class of drugs. If not, another class of drugs will be given, or possibly exogenous supplies of the deficient enzyme will be furnished; but all this is still in the future—today's pharmacologic science fiction.

While there is little doubt that certain cutaneous drug reactions arise because of an allergic mechanism—for example, contact dermatitis to ammoniated mercury or urticaria from penicillin—I believe that many so-called allergic skin-drug reactions do not develop because of an allergy but are in reality examples of deviation. In my opinion fixed drug eruptions—iododermas, bromodermas, and toxic epidermal necrolysis in the adult—develop because of deviation. When the pharmacologist speaks of

deviation he means biochemical deviation, and there is abundant evidence to support this; but I would hypothesize that anatomical deviations could also conduce to the development of altered or deviant reactions to a drug. It is conceivable that persons who develop bromoderma have an anatomically deviant sweat or pilosebaceous apparatus which makes them more vulnerable to the cutaneous excretion of these drugs.*

The term id was first used as a suffix by Jean Darier in 1896, when he applied it to skin lesions which he termed "tuberculids." He used the term in the belief that the skin lesions so designated arose because of cutaneous irritation developing in response to toxins emanating from a tuberculous focus. Approximately 15 years later, Josef Jadassohn applied the term id to eruptions developing in connection with ringworm infection. He hypothesized that the lesions developed because the host had become allergic to the fungus or to products derived from it. When these products were distributed from the focus and lodged in the skin an allergic reaction ensued which he labeled "dermatophytid." There is no doubt that this concept achieved great popularity; the term id is today a much used but even more abused label. It seemingly denotes a variety of skin lesions allegedly developing because of an allergic reaction to products emanating from a focus of infection. Unfortunately, there is almost no evidence to support this hypothesis, and many logical arguments can be advanced against it. For example, if the ids from a dermatophytic infection arise because of an allergic reaction to products emanating from the infectious focus, it is difficult to explain why they are confined to the skin. It is easy to explain why the infection is confined to the skin. This is so because the dermatophytic fungi have nutritional requirements that do not enable them to exist within the body; but for an allergic reaction contingent upon them, this argument does not hold. In allergic reactions of delayed hypersensitivity—and this is the type of hypersensitivity allegedly underlying the id reaction—all the tissues of the body can and do participate, because the reaction is dependent on interaction between the allergen and appropriate lymphocytes which circulate everywhere. Further, it is hypothesized by the proponents of the allergic view for ids that the allergen is carried in the blood. Consequently, there is no a priori reason for believing that a fungus particle would not lodge in the spleen, liver, or kidney where, in the allergic host,

*Rostenberg, A., Jr.: *Drug Reactions.* Excerpta Medica International Congress Series No. 55. Proc. XII International Congress of Dermatology, Washington, D.C., September 1962, pp. 1087-94.

it could meet an appropriate lymphocyte. The allergic reaction should then develop at that site. Yet there has never been any evidence that this happens.

Finally, let us turn to atopic dermatitis, which I have labeled a nonallergic allergic condition. There is no better example of the deadening influence of a label on medical thinking than this. At the time it was so christened it was thought that the lesions were the cutaneous analogues of asthma and hay fever and that they arose through a similar immunologic mechanism; however, the only evidence for the atopic nature of this condition is that most persons who have it are atopic individuals. There is not a scintilla of evidence to show that the cutaneous lesions are brought about by an immunologic mechanism, and there is much evidence against it.

With respect to any view or position "there is no greater infidelity to the pioneers of the past than the refusal to budge from the position they took." Actually, the fundamental defect in atopic dermatitis is, I believe, a genetically determined anomaly of the skin that makes it highly vulnerable to pruritic stimuli, and as a consequence of the scratching so induced it lichenifies.* The French realized this almost 100 years ago; as Jacquet felicitously said, "It is not the eruption that is pruritic, but it is the pruritus that is eruptive."

Despite the fact that no evidence has been added to show the atopic nature of this condition and despite the fact that desensitization accomplishes nothing for the skin lesions, the belief in its atopic nature lingers on. Unfortunately, outworn medical ideas have an even greater vitality than old generals; they not only do not die, but neither do they fade away.

*Rostenberg, A., Jr.: Atopic Dermatitis: A Discussion of Certain Theories Concerning its Pathogenesis. In: *Atopic Dermatitis,* Baer, R. L., editor. Philadelphia, Lippincott, 1956.